

Heart in Fabry Disease

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Abstract

Fabry disease is one of the lysosomal storage disorders, that results from progressive multiorgan accumulation of glycoproteins. It is caused by mutations of the GLA gene, which encodes alpha-galactosidase A. The incidence of Fabry disease is estimated at the level of 1:55 000 male births, however the true prevalence, including atypical, sub-clinical or late-variant phenotypes may be higher. Typically, early manifestations of the disease, neuropathy and angiokeratomas, are evident by youth. Cardiac involvement results in left ventricle hypertrophy, although lysosomal deposits may lead to conduction disorders, coronary artery disease, aortic and mitral valve insufficiency. This review presents detailed description of Fabry disease pathophysiology, genetics and epidemiology. It provides the latest data on screening, diagnostics and management. JRCD 2012; 1: 3–6

Key words: Storage disease; Myocardial hypertrophy

Genetic, epidemiologic and symptomatic background

Fabry disease is one of the 40 lysosomal storage disorders, that results in the progressively destructive accumulation of glycoproteins in multiorgan localization [1-3]. Also called Anderson-Fabry disease, it is caused by mutations in the galactosidase alpha (GLA) gene, which encodes important metabolic enzyme alpha-galactosidase A. This enzymatic defect results in accumulation of unmetabolized substrate i.e. glycosphingolipids, specifically globotriaosylceramide, within the lysosomes.

From genetic-epidemiologic point of view there are several important observations to make. Firstly, despite an X-linked heritage, heterozygous females apart from hemizygous males can also be affected phenotypically. Secondly, an atypical variant of Fabry disease, which presents as cardiac hypertrophy (mimicking hypertrophic cardiomyopathy) in middle-aged subjects has been identified [4]. The mechanisms of the cardio-tropism of the cardiac variant of Fabry has not been discovered. Thirdly, the incidence of Fabry disease (as a rare disease) is initially estimated to be 1:55 000 male births [1]. However, due to the various constellations of presented symptoms as well as diversity of mutations allowing limited (but not absolutely absent) alpha-galactosidase A activity, the actual incidence of Fabry, including atypical, sub-clinical or late-variant phenotypes is likely to be much higher, even as high as 1:3100 male births [5].

The progressively destructive storage leads to multiorgan cellular dysfunction. The most frequently involved organs include kidneys, heart, peripheral nerves and skin [1–3]. Multidisciplinary manifesta-

tions of Fabry disease are directly related to the accumulation of glycosphingolipids in tissues with their spectrum dependent upon age. Firstly in childhood, symptoms usually present with painful neuropathy of hands and feet (acroparesthesia), nausea and abdominal pain. Later in life a skin marker of the disease occurs, namely angiokeratomas. Angiokeratomas are formed by invasion of enlarged cutaneous capillaries, specifically of the trunk, and they increase in number and size with age. Proteinuria manifests kidney involvement, and thus herald kidney dysfunction. Eventually, renal failure results from multifocal and multilevel accumulation of glycosphingolipids in the tubular epithelial, glomerular and endothelial cells, causing glomerulosclerosis and microvascular dysfunction. As regards to prognosis, males progress to renal failure by their fourth decade and females by their fifth decade, if untreated [6] Cerebrovascular complications including transient ischemic attacks (minor symptom) and strokes (major symptom) are 12 times more common, than the general population in males between the ages of 25 and 44. Broad spectrum of other neurological symptoms include decreased hearing, anhidrosis, abnormal peripheral sensation such as impaired temperature perception, pin-pricks or neuropathic pain (acroparesthesia). Additionally, Fabry-specific corneal opacities can develop, although usually not affecting the normal clearance of vision.

Cardiac complications seem to be particularly important. Manifestations of heart involvement include several symptoms: palpitations, dyspnoea or angina, usually secondary to an arrhythmia or myocardial hypertrophy. Cardiac involvement may also be present early in life but is usually not manifested clinically until the third or fourth decade. Cardiovascular involvement contributes to substantial morbidity and premature death from heart failure, arrhythmia

or stroke. From the clinical point of view, females are not 'silent carriers' and may also be affected with cardiac manifestations [7].

Cardiac involvement

Screening among patients with left ventricular hypertrophy (especially with hypertrophic cardiomyopathy)

Accumulating globotriaosylceramide (Gb3) induces destruction in key-important tissue of the heart i.e. cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells, and vascular smooth muscle cells [1-3]. The most visible result of storage process is the left ventricular hypertrophy (LVH), which, including pretentative diagnosis of hypertrophic cardiomyopathy, may herald Fabry disease. Surprisingly, the chronic accumulation of Gb3 in the heart contributes only minimally (1% to 2% of the total cardiac mass) and hence does not directly account for the degree of LVH [8,9]. Intriguingly, it is postulated, that hypertrophy resulted from "irritating response" is mediated by accumulated Gb3 infiltrative materials triggering intracellular signaling pathways leading to hypertrophy, apoptosis, necrosis and fibrosis. Therefore, Fabry cardiomyopathy could be considered a 'pseudo'-hypertrophic cardiomyopathy, in which secondary hypertrophy plays more prominent role than restrictive physiology in contributing to the heart failure. A number of studies, each using different screening methods, have attempted to determine the prevalence of Fabry disease in patients with LVH. Nakao *et al.* [4] screened 230 male patients with LVH and reported 7 cases (3%) with low plasma α -galactosidase A activity. Pathogenic mutations were identified in 2 patients, and the remainder had markedly reduced α -galactosidase A messenger RNA levels. A subsequent study by Sachdev *et al.* [10] examined plasma α -galactosidase A activity in 153 male patients with hypertrophic cardiomyopathy and found that 3.9% had abnormally low levels. Fabry disease was subsequently confirmed by genetic analysis in all cases. More recently, Monserrat *et al.* [11] screened for plasma α -galactosidase A activity in a larger cohort of 508 patients (328 male, 180 female) with hypertrophic cardiomyopathy. Low plasma α -galactosidase A activity was observed in 15 patients (3%). As regards to females, Chimenti *et al.* [12] screened 34 women with hypertrophic cardiomyopathy by biventricular endomyocardial biopsy as well as plasma α -galactosidase A activity. In this exclusively female cohort, 4 patients (12%) had histologic features diagnostic of Fabry disease and pathogenic mutations. Although concentric left ventricular hypertrophy is the most typical pattern, asymmetric septal hypertrophy (more commonly configuration seen in classic hypertrophic cardiomyopathy caused by sarcomere protein gene mutations) accounts for some portion of cases [1-3]. Apart from LVH, Fabry patients developed second feature mimicking hypertrophic cardiomyopathy i.e. left ventricular outflow tract gradient especially after stimulation by exercise [13,14]. Exercise-provocable left ventricular outflow tract gradient has frequently developed in HCM [15,16].

Left ventricular function – echocardiography, cardiovascular magnetic resonance (CMR)

Despite common LVH, the mean ejection fraction was preserved in majority of patients [17]. Contrary, mild to moderate LV diastolic dysfunction is often present [14] mainly manifested by impaired left ventricle (LV) relaxation. A smaller proportion of patients has a pseudonormal filling pattern but restrictive physiology is rare [18]. Early cardiac involvement may be effectively detected by echocardiography with tissue Doppler imaging. In a preclinical study disease mutation carriers had reduced systolic (Sa), early (Ea), and late (Aa) diastolic velocities at the lateral and septal aspects of the mitral annulus [18]. Tissue Doppler imaging parameters deteriorated with an increase of LV wall thickness [19]. More detailed analysis of myocardial function and morphology is possibly by CMR. This novel method provides complementary data to echocardiography through its ability to characterize tissue structure using contrast agent i.e. gadolinium enhancement. Correlation of histologic findings from autopsy with magnetic resonance images obtained before death has shown that late gadolinium enhancement is caused by myocardial collagen deposit [20].

The progression of myocardial abnormalities is gender and age dependent and distinct pattern of disease development was reported in genetically- or biopsy-proven cases of Fabry disease [21]. Generally, no patient had late gadolinium enhancement (LGE) without LVH. Males without LVH had reduced longitudinal function in the lateral wall and septum, whereas males with LVH but without LGE also had reduced radial function. Males with LVH and LGE had severe longitudinal and radial dysfunction [21]. Females younger than 20 years old had apparently normal findings no evidence of hypertrophy, normal radial and longitudinal function and no LGE. Older women but still without LVH had reduced longitudinal function isolated to the lateral wall of the left ventricle. Women with LVH had reduced longitudinal and radial function and finally women with LVH and LGE had severely reduced longitudinal and radial function.

Summarizing these data, global LV function was preserved, functional abnormalities detected by tissue Doppler arose before hypertrophy, and fibrosis was visible on CMR only after hypertrophy developed.

Coronary circulation

Abnormalities in coronary vasculature have been detected both in macro-(epicardial) and microcirculation level. From clinical point of view, many patients especially those with LV hypertrophy, complain of typical signs of angina suggestive of myocardial ischemia [14,22]. Despite the high incidence of ischemic symptoms and the diffuse arteriopathy that affects the endothelium, intima, media, and adventitia of blood vessels, the epicardial coronary arteries are significantly stenosed only in a minority [23]. However, despite the lack of significant coronary artery disease on angiograms diffuse hypo-echogenic plaques were relatively frequent.

The several mechanism of ischemia may include: increased myocardial oxygen demand (due to LVH), endothelial dysfunction and microvascular dysfunction with impaired myocardial blood flow and reduced coronary flow reserve [24,25].

Conduction abnormalities and arrhythmias

Accumulation of Gb3 may disturb conduction system both by acceleration or deceleration of impulse conductance. A short PR interval is seen in 40% of patients [26] and is caused by accelerated atrioventricular (AV) conduction rather than by accessory pathways [27,28]. This abnormality may be defined as pseudo-preexcitation pattern. Accelerated AV conduction is thought to be more common in younger patients without LVH, whereas older patients are more likely to develop progressive AV conduction delay with bradycardia and chronotropic incompetence [29].

Gb3 has generated arrhythmogenic substrate where atrial arrhythmias are more common than ventricular arrhythmias. In a case series of 78 patients over 10 years, 13% had paroxysmal atrial fibrillation (which was four times that of the general population for age) and 8% had non-sustained ventricular tachycardia [30]. Importantly, all these patients with ventricular tachycardia had LVH. Ventricular arrhythmia refractory to internal defibrillator shocks has been reported in a patient with severe concentric hypertrophy [31].

Valvular defect

Gb3 infiltration and deposition in heart valve tissue with secondary fibrosis and calcification can lead to valvular dysfunction [1]. In several patients, hypertrophy of papillary muscles and/or systolic anterior motion of the mitral leaflets associated with LV outflow obstruction may aggravate the mitral valve dysfunction. Previous studies have shown predominantly mild regurgitation in aortic, mitral, and tricuspid valves [32,33]. In this series of patients only two subjects showed mild aortic valve stenosis. In larger group of patients from Fabry outcome survey registry, valve disease was reported in 14.6% of subjects, but valve surgery was infrequent suggesting that the lesions are rarely of hemodynamic significance [22].

Effect of enzyme replacement therapy on cardiovascular system

Enzyme replacement therapy beneficially reduces Gb3 levels in cardiac tissue and especially in vascular endothelial cells. Several observational studies were focused specifically on cardiac endpoints in Fabry patients on substitutive therapy. Several studies have documented statistically significant reduction in LVH by echocardiography [22,34] and CMR [35,36]. On microscopic scale Hughes *et al.* document a 20% decrease in myocardial Gb3 content by cardiac biopsy at six months of therapy, versus a 10% increase in patients receiving placebo [36]. At least one study has documented an improvement in diastolic dysfunction (29% decrease of E/Ea), although there was no improvement in LVH or renal function [37]. Hypothetically, this lack of efficacy may be due to the degree of fibrosis. Accordingly, recent study have documented a statistically significant reduction in LVH, improved myocardial function by tissue Doppler imaging and improved exercise capacity in patients with no fibrosis by late gadolinium enhancement. However, in patients with mild or severe fibrosis, there was only minimal improvement in LVH and no improvement in LV function or exercise capacity [38].

As regards to electrophysiological abnormalities there is a few data on the prevalence of arrhythmias with and without treatment,

however incidental episode of the lengthening of a 'short PR interval' after treatment was reported [39].

In short-term follow-up, enzyme replacement therapy does not seem to improve coronary blood flow. In one study, coronary microvascular dysfunction failed to recover in 5 male patients (mean age, 59 years) after 10 months of treatment [36]. A subsequent study of 10 younger patients (mean age, 34 years) also failed to show any effect [40]. Coronary microcirculation dysfunction does not appear to improve on therapy, nor does angina improve despite improvement in LVH however, this may be confounded by the degree of cardiac involvement. Alternatively longer period of treatment may be needed before microvascular dysfunction improves with therapy.

Based on limited data from small studies, it appears that treatment should be initiated early, ideally before the development of fibrosis (late gadolinium hyperenhancement). CMR-guided therapy may appeared optimal approach.

Summary

Cardiac involvement is a common feature of Fabry disease and should be considered in the differential diagnosis of patients presenting with unexplained left ventricular hypertrophy. Cardiac involvement is associated with significant cardiovascular morbidity and mortality. There is growing evidence that enzyme replacement therapy helps halt progression and possibly reverses cardiac disease in some patients. Screening of asymptomatic relatives provides an opportunity to detect preclinical disease and institute treatment to prevent life-threatening long-term complications. Cardiologists may play a key role in suspecting and diagnosing Fabry disease.

Conflict of interest: non declared.

References

- Linhardt A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart* 2007; 93: 528–535.
- Zarate YA, Hopkin RJ. Fabry's disease. *Lancet* 2008; 372: 1427–1435.
- O'Mahony C, Elliott P. Anderson-Fabry disease and the heart. *Prog Cardiovasc Dis.* 2010; 52: 326–335.
- Nakao S, Takenaka T, Maeda M, *et al.* An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *New Eng J Med* 1995; 333: 288–293.
- Spada M, Pagliardini S, Yasuda M, *et al.* High incidence of later-onset Fabry disease revealed by newborn screening. *Am J Hum Genet* 2006; 79: 31–40.
- Schiffmann R, Warnock DG, Banikazemi M, *et al.* Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant.* 2009; 24: 2102–2111.
- Vedder AC, Linthorst GE, van Breemen MJ, *et al.* The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels. *J Inher Metab Dis* 2007; 30: 68–78.
- Elleder M, Bradova V, Smid F, *et al.* Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. *Virchows Arch A Pathol Anat Histopathol* 1990; 417: 449–455.
- Elleder M. Sequelae of storage in Fabry disease—pathology and comparison with other lysosomal storage diseases. *Acta Paediatr Suppl* 2003;92:46–53.
- Sachdev B, Takenaka T, Teraguchi H, *et al.* Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002; 105: 1407–1411.
- Montserrat L, Gimeno-Blanes JR, Marin F, *et al.* Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2007; 50: 2399–2403.

12. Chimenti C, Pieroni M, Morgante E, *et al.* Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation* 2004; 110: 1047–1053.
13. Calcagnino M, O'Mahony C, Coats C, *et al.* Exercise-induced left ventricular outflow tract obstruction in symptomatic patients with anderson-fabry disease. *J Am Coll Cardiol.* 2011; 58: 88–89.
14. Linhart A, Lubanda JC, Palecek T, *et al.* Cardiac manifestations in Fabry disease. *J Inherit Metab Dis.* 2001; 24 (Suppl 2): 75–83.
15. Dimitrow PP, Cheng TO. Standing position alone or in combination with exercise as a stress test to provoke left ventricular outflow tract gradient in hypertrophic cardiomyopathy and other conditions. *Int J Cardiol.* 2010; 143: 219–222.
16. Dimitrow PP, Bober M, Michałowska J, *et al.* Left ventricular outflow tract gradient provoked by upright position or exercise in treated patients with hypertrophic cardiomyopathy without obstruction at rest. *Echocardiography.* 2009; 26: 513–520.
17. Pinderski LJ, Strotmann J: Congestive heart failure in Fabry cardiomyopathy: Natural history experience in an international cohort of 1,448 patients. *J Heart Lung Transplant* 2006; 25: 70.
18. Pieroni M, Chimenti C, Ricci R, *et al.* Early detection of Fabry cardiomyopathy by tissue Doppler imaging. *Circulation* 2003; 107: 1978–1984.
19. Pieroni M, Chimenti C, Russo A, *et al.* Tissue Doppler imaging in Fabry disease. *Curr Opin Cardiol* 2004; 19: 452–457.
20. Moon JC, Sheppard M, Reed E, *et al.* The histological basis of late gadolinium enhancement cardiovascular magnetic resonance in a patient with Anderson-Fabry disease. *J Cardiovasc Magn Reson* 2006; 8: 479–482.
21. Weidemann F, Breunig F, Beer M, *et al.* The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. *Eur Heart J* 2005; 26: 1221–1227.
22. Linhart A, Kampmann C, Zamorano JL, *et al.* Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007; 28: 1228–1235.
23. Kovarnik T, Mintz GS, Karetova D, *et al.* Intravascular ultrasound assessment of coronary artery involvement in Fabry disease. *J Inherit Metab Dis* 2008; 31: 753–760.
24. Elliott PM, Kindler H, Shah JS, *et al.* Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. *Heart* 2006; 92: 357–360.
25. Dimitrow PP, Krzanowski M, Undas A. Reduced coronary flow reserve in Anderson-Fabry disease measured by transthoracic Doppler echocardiography. *Cardiovasc Ultrasound.* 2005; 3: 11.
26. Senechal M, Germain DP. Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. *Clin Genet* 2003; 63: 46–52.
27. Pochis WT, Litzow JT, King BG, *et al.* Electrophysiologic findings in Fabry's disease with a short PR interval. *Am J Cardiol* 1994; 74: 203–204.
28. Jastrzebski M, Bacior B, Dimitrow PP, Kawecka-Jaszcz K. Electrophysiological study in a patient with Fabry disease and a short PQ interval. *Europace.* 2006; 8: 1045–1047.
29. Lobo T, Morgan J, Bjorksten A, *et al.* Cardiovascular testing in Fabry disease: exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement. *Intern Med J* 2008; 38: 407–414.
30. Shah JS, Hughes DA, Sachdev B, *et al.* Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. *Am J Cardiol* 2005; 96: 842–846.
31. Eckart RE, Kinney KG, Belnap CM, *et al.* Ventricular fibrillation refractory to automatic internal cardiac defibrillator in Fabry's disease. Review of cardiovascular manifestations. *Cardiology* 2000; 94: 208–212.
32. Weidemann F, Strotmann JM, Niemann M, *et al.* Heart valve involvement in Fabry cardiomyopathy. *Ultrasound Med Biol.* 2009; 35: 730–735.
33. Linhart A, Palecek T, Bultas J, *et al.* New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J.* 2000; 139: 1101–1108.
34. Spinelli L, Pisani A, Sabbatini M, *et al.* Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. *Clin Genet* 2004; 66: 158–165.
35. Beer M, Weidemann F, Breunig F, *et al.* Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. *Am J Cardiol* 2006; 97: 1515–1518.
36. Hughes DA, Elliott PM, Shah J, *et al.* Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008; 94: 153–158.
37. Kovacevic-Preradovic T, Zuber M, Jost CH, *et al.* Anderson-Fabry disease: long-term echocardiographic follow-up under enzyme replacement therapy. *Eur J Echocardiogr* 2008; 9: 729–735.
38. Weidemann F, Niemann M, Breunig F, *et al.* Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation* 2009; 119: 524–529.
39. Waldek S. PR interval and the response to enzyme-replacement therapy for Fabry's disease. *N Engl J Med* 2003; 348: 1186–1187.
40. Kalliokoski RJ, Kantola I, Kalliokoski KK, *et al.* The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. *J Inherit Metab Dis* 2006; 29: 112–118.